A retrospective cross-sectional study of adherence to adjuvant endocrine treatment in women 36-56yrs with a hormone receptor-positive breast cancer: Patient compliance and impact on prognosis

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BACKGROUND & AIMS

- 80% of breast cancer cases are hormone receptor-positive, AET is a cornerstone of treatment.[1]
- Poor adherence-rates are associated with increased recurrence rates, reduced disease-free survival and overall survival, reduced QoL.[2]

We aim to evaluate:

1. **Evolution of AR over time, impact of treatment duration on AR in Belgium**
2. **The impact of patient adherence on clinical outcomes (OS, RFS)**
3. **How adherence is influenced by patient-, disease and treatment characteristics**

PATIENTS, DATA & METHODS

Study population

- All patiënts aged 36-56 years diagnosed with high-risk early HR+ breast cancer who started adjuvant treatment at UZ Leuven between 2008 and 2018 (see figure 1)

Data

- Clinical and treatment data are retrieved from UZ Leuven records.
- Medication retrieval data from both public and hospital pharmacies obtained using national insurance databases (IMA, farmanet and Healthcare)

Methods

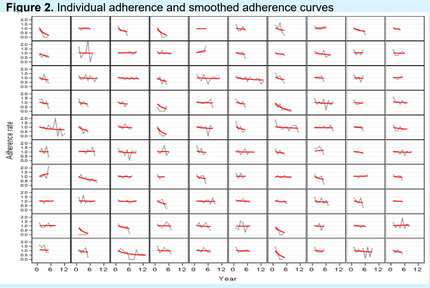
- Adherence is defined as the medication-possession ratio (MPR) = proportion of prescribed medication obtained over time.
- Smoothed adherence trajectories (see figure 2) are derived
- Percentage of poor/non-adherence over time estimated:
  - Poor adherence = MPR < 95%
  - Non-adherence = MPR < 80%
- Analysis of survival outcomes presented as hazard ratios.
- Events counted after determination of AR to avoid immortality time bias. Survival analyses are corrected for age.
- Associations between adherence and clinical/demographic variables explored (Age, pN, grade, BMI and AET at start)

Patient characteristics

Figure 1. Characteristics of the study population collected from the medical records of UZ Leuven.

Variable		Patients included (n = 649), n (%, range)
Patient characteristics		
Mean age		48 (36-56)
Menopausal status at diagnosis	Premenopausal	481 (74.1)
	Postmenopausal	141 (21.7)
	Missing	27 (4.1)
BMI	BMI < 25	368 (56.7)
	BMI 25-30	188 (28.9)
	BMI > 30	93 (14.3)
Tumor characteristics		
Grade	1	32 (4.9)
	2	340 (52.4)
	3	277 (42.7)
Nodal status, pN	0	248 (38.2)
	+	401 (61.8)
HER2 positive		128 (28)
Treatment characteristics		
Type of AET suggested for first 5y by MDT	5j AI	223 (34.4)
	5j TAM	208 (32)
	5j AI + OFS	30 (4.6)
	Switch TAM - AI	188 (29)
Ovarian function suppression (OFS)		99 (15.3)
Chemotherapy	Neoadjuvant	51 (7.6)
	Adjuvant	598
Breast cancer specific outcomes		
Breast cancer recurrence	Local	14 (2.6)
	Metastasis	45 (6.9)
Death by breast cancer		19 (2.9)

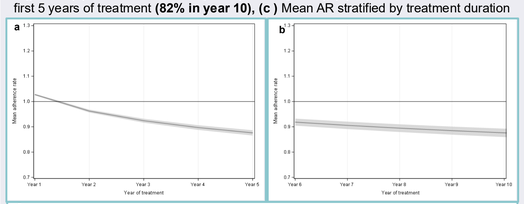
Figure 2. Individual adherence and smoothed adherence curves



Results

Adherence rate

Figure 3. (a) Overall AR in first 5 years **(88% in year 5), (b)** Overall adherence rate after first 5 years of treatment **(82% in year 10), (c)** Mean AR stratified by treatment duration



c Mean adherence rate (95% CI) by treatment duration

Year of treatment	1 year	2 years	3 years	4 years	5 years
Year 1	1.021 (0.979;1.063)	0.992 (0.955;1.030)	1.027 (0.995;1.060)	1.009 (0.981;1.038)	1.020 (1.015;1.024)
Year 2		0.933 (0.869;0.996)	0.974 (0.915;1.033)	0.915 (0.862;0.967)	0.914 (0.906;0.923)
Year 3			0.943 (0.866;1.020)	0.860 (0.790;0.929)	0.853 (0.842;0.864)
Year 4				0.820 (0.738;0.903)	0.809 (0.797;0.822)
Year 5					0.776 (0.761;0.790)

Year of treatment	6 years	7 years	8 years	9 years	>=9 years
Year 1	1.035 (1.026;1.044)	1.036 (1.025;1.046)	1.042 (1.033;1.052)	1.033 (1.024;1.042)	1.031 (1.024;1.039)
Year 2	1.017 (1.002;1.033)	0.994 (0.978;1.009)	1.004 (0.991;1.016)	1.006 (0.995;1.017)	0.988 (0.980;0.996)
Year 3	1.007 (0.986;1.028)	0.969 (0.948;0.990)	0.981 (0.965;0.997)	0.991 (0.977;1.005)	0.963 (0.954;0.973)
Year 4	1.000 (0.975;1.024)	0.951 (0.927;0.976)	0.965 (0.946;0.984)	0.980 (0.963;0.996)	0.945 (0.934;0.957)
Year 5	0.994 (0.966;1.022)	0.938 (0.910;0.965)	0.953 (0.931;0.974)	0.971 (0.953;0.989)	0.932 (0.919;0.944)
Year 6		0.927 (0.896;0.957)	0.943 (0.919;0.966)	0.964 (0.944;0.984)	0.920 (0.907;0.934)
Year 7				0.958 (0.937;0.980)	0.911 (0.896;0.925)
Year 8				0.953 (0.930;0.976)	0.902 (0.887;0.918)
Year 9					0.895 (0.879;0.911)
Year 10					0.889 (0.872;0.905)

Probability of poor- and non-adherence

Figure 4. Probability of poor adherence (<95%) in the first 5 years (a) and after 5 years (b) **(55.9% in year 5, 60.1% in year 10)**

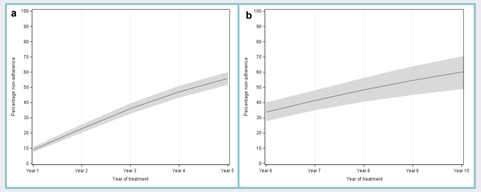
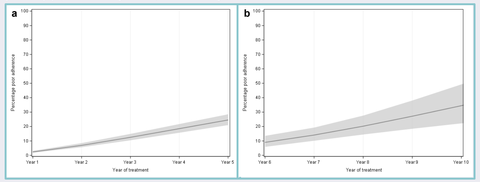


Figure 5. Probability of non-adherence (<80%) in the first 5 years (a) and after 5 years (b) **(24.6% in year 5, 34.5% in year 10)**



Covariate effects on adherence

Figure 6. BMI (<25, 25-30, >30)

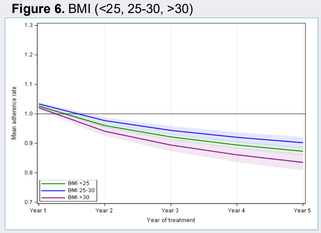


Figure 7. Age (<45y, >= 45y)



Figure 8. Tamoxifen as first product

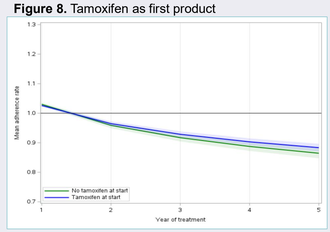


Figure 9. Tumor grade (1, 2, 3)

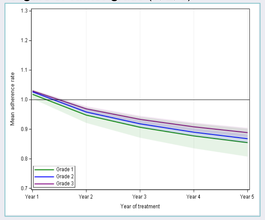
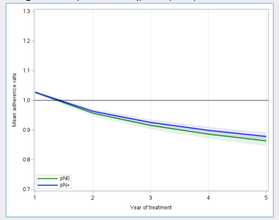


Figure 10. pN status (pN0, pN+)



- **Tumor grade, pN status** did not show statistically significant effect on AR
- **Age** had a significant overall effect on AR (main effect p = 0.0412)
- AR's evolved differently over time depending on whether patients **started treatment with tamoxifen** (interaction p = 0.0139) and overall adherence differed significantly between groups (p = 0.0320)
- **BMI** significantly influenced adherence over time (interaction p = 0.0011). Patients with obesity (BMI>30) experienced a steeper decline in adherence, reaching 83.5% by year 5, compared to 90.2% in those with BMI 25-30.

Impact of adherence on oncological outcomes (OS, RFS)

Figure 11. (a) AR as a continious predictor for overall survival, (b) non-adherence as a predictor for recurrence free survival

a Adherence rate as continuous predictor for overall survival

Outcome	Effect	Hazard Ratio (95% CI)	P-value	N patients	N events
OS since year 1	Adherence rate in years <=1 (+1%)	0.972 (0.890;1.062)	0.5287	626	28
OS since year 2	Adherence rate in years <=2 (+1%)	1.029 (0.955;1.107)	0.4544	617	24
OS since year 3	Adherence rate in years <=3 (+1%)	1.040 (0.974;1.109)	0.2388	563	20
OS since year 4	Adherence rate in years <=4 (+1%)	1.052 (0.986;1.122)	0.1235	501	14
OS since year 5	Adherence rate in years <=5 (+1%)	1.031 (0.972;1.093)	0.3141	432	11

b Non-adherence (<80%) as predictor for recurrence free survival

Outcome	Effect	Hazard Ratio (95% CI)	P-value	N patients	N events
RFS since year 1	In years <=1: poor adherence (<80%) vs good adherence (>=80%)	-	0.8440	624	60
RFS since year 2	In years <=2: poor adherence (<80%) vs good adherence (>=80%)	-	0.3424	612	49
RFS since year 3	In years <=3: poor adherence (<80%) vs good adherence (>=80%)	-	0.2145	555	37
RFS since year 4	In years <=4: poor adherence (<80%) vs good adherence (>=80%)	0.946 (0.283;3.155)	0.9275	497	29
RFS since year 5	In years <=5: poor adherence (<80%) vs good adherence (>=80%)	0.356 (0.048;2.667)	0.3151	428	21

- **No significant HR's for RFS or OS in function of adherence** as a continuous or categorical variable (poor- or non-adherence) were found.
- Median follow-up was 7.6 years

CONCLUSION

- **Steady annual adherence decline; 55.9% poor adherent at year 5**
- **No impact of adherence on survival outcomes detected -> longer follow-up needed**
- **High BMI was a significant predictor of steeper adherence decline**

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ABBREVIATIONS

AIs: aromatase inhibitors, AET: adjuvant endocrine therapy, AR: adherence-rate, BMI: body mass index, CI: confidence interval, GEE: generalized estimating equations, HR+: hormone-receptor positive, IMA: intermutualistisch agentschap, MPR: medication-possession ratio, OS: overall survival, RFS: recurrence-free survival

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